Cysticercosis Update

JAMES SANTIAGO GRISOLIA, MD, *San Diego*

Already the most common brain parasite disease, cysticercosis has been increasingly seen throughout the American Southwest. Symptoms arise from infection with larvae of Taenia solium, *the pork tapeworm. Seizures, hydrocephalus, focal deficits and chronic meningitis most commonly result. Cerebrospinal fluid eosinophilia, serology by indirect hemagglutination and computed tomography are helpful adjuncts to diagnosis. New evidence suggests that selective immunosuppression is important for the parasites' survival and that cyst death permits renewed host immunity, which may actually precipitate an acute neurologic presentation. New larvicides, including praziquantel, are being tested in humans; caution is indicated in assessing these drugs because of the acute worsening associated with cyst death. Conventional therapy includes anticonvulsants, steroids or ventricular drainage as needed. Prevention remains the best management. Person-to-person transmission within the United States has recently been documented and merits public health scrutiny.*

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Cysticercosis has long been the most important central nervous system parasitic disease in the Third World but is only now achieving significant impact in the United States. In the past decade, hospitals throughout the Southwest have seen increasing numbers of cases, as attested to by several recent clinical series.[1-6] Immigration from Mexico and other endemic areas accounts for the rising incidence of cysticercosis in California and other states. In 1980 there were 4.5 million Mexicans and Chicanos living in California. Nationally, the Mexican-descended population increased from 4.5 million in 1970 to 8.7 million in 1980, with a trend towards wider distribution across the country.[7] There is now evidence of transmission of the disease between persons living within the United States.[2,8] Clinical findings in cases of cysticercosis and its laboratory diagnosis are detailed in recent reports[1,2]; this review focuses on new concepts in pathogenesis and implications for therapy.

Cysticercosis is the systemic infection with the larval stage of *Taenia solium*, the pork tapeworm. The normal life cycle of *T solium* alternates between human tapeworm infestation and swine cysticercosis. Tapeworm eggs passed in infected human feces are eaten by pigs. In the pig intestine the eggs release embryos that burrow into the mucosal wall and enter the bloodstream, ending as encysted larvae (cysticerci) in multiple organs, chiefly muscle and brain. When humans eat poorly cooked, infected pork, the larvae attach in the gut lumen and become adult tapeworms, thus completing the cycle. Human cysticercosis results when humans become infected with the eggs through fecal-oral contamination or an equivalent mechanism (Figure 1).

Central nervous system lesions usually occur in the cerebral parenchyma, subarachnoid cisterns and ventricles. The larvae typically live for several years, then die, often with a dense local inflammatory response. Onset or exacerbation of symptoms may coincide with cyst death.[9] With time, the dead cysts may calcify.

Clinical manifestations depend on where the cysticerci become established. Muscle lesions usually cause no symptoms, though a painful myositis can result. Cortical lesions may produce seizures or focal neurologic deficits, or both. Ventricular lesions result in a noncommunicating hydrocephalus, occasionally with a ball-valve mechanism causing syncope due to sudden complete blockage.[2] Cisternal lesions cause a chemical meningitis (which may present with an acute, subacute or chronic course), communicating hydrocephalus, cranial nerve palsies or dementia. True strokes may re-

From the Departments of Neurosciences, University of California, San Diego, and Mercy Hospital and Medical Center, San Diego.
Submitted, revised, September 26, 1983.
Reprint requests to James Grisolia, MD, 4020 Fifth Avenue, Suite 404, San Diego, CA 92103.

sult if this inflammation thromboses a cerebral vessel, though sudden focal deficits may also result from strictly parenchymal cysts, presumably without a vascular basis. Rarely, cyst lesions may mimic numerous other syndromes.[1]

Screening laboratory studies are not helpful. Examination of a cerebrospinal fluid specimen may show any pattern, mimicking a bacterial or an aseptic meningitis or even appearing normal with some ventricular or deep parenchymal lesions. Findings such as increased γ-globulin levels can mimic multiple sclerosis or any chronic infection. Cerebrospinal fluid eosinophilia may be found with a Wright's or an eosinophil stain (*not* with routine differential by a counting chamber), which is highly suggestive but not diagnostic.[10] Serology by indirect hemagglutination may be carried out on serum or cerebrospinal fluid specimens through the Centers for Disease Control. It is positive in 60% to 80% of all patients,[2] with fewer false-negatives in the meningitic or acute parenchymal forms and almost no false-positives except in other parasitic infections,[11] especially echinococcosis.[12] Serology done on serum specimens appears more sensitive than that on cerebrospinal fluid. Other serologic studies are under investigation.[13]

Computed tomographic (CT) findings have been well documented.[14-16] Depending on the state of infection, parenchymal lesions may be invisible, cystic, hypodense (with or without contrast enhancement) or calcified. Ventricular lesions may cause focal hydrocephalus and often require CT ventriculography for precise delineation.[17] Ventricular cysts may move if a patient changes position. Subarachnoid lesions may be associated with extra-axial cysts, basilar cisternal contrast enhancement or, most commonly, hydrocephalus. Other radiologic studies including plain films of skull or soft tissues, angiography and so forth are usually not helpful.

Currently, the diagnosis rests on clinical criteria bolstered by epidemiologic (Mexican or other endemic exposure) and laboratory (serology, CT scan or biopsy) findings. No single test can either "rule out" the diagnosis or completely exclude other diseases.

Conventional therapy is symptomatic, including anticonvulsants, steroids or ventriculoperitoneal shunting as needed. Surgical excision is rarely required. The best management is prevention by adequate sanitation and by vigorously searching for and treating tapeworm infestation. A variety of larvicidal agents are under investigation.

New concepts are emerging from recent clinical experience and laboratory investigation. The normal life cycle of cysticerci demonstrates surprising efficiency, with sites of predilection that confer enormous selective advantage—that is, muscle (thus maximizing transmission to other carnivores) and brain (enhancing a pig's vulnerability to predation). This apparent efficiency actually arises from complex host-parasite interactions, and recent observations shed important light on the pathogenesis of infection and clinical disease.

Many cysticercotic patients have no detectable immune response to cysticercal antigens.[18] This intriguing observation has led to the concept of selective immunosuppression of the host by the parasites, much as has been documented in cases of filariasis.[19] In experimental infections with various species of *Taenia,* parasite factors have been identified that can deplete complement, suppress lymphocyte activity, reduce eosinophil activity, kill granulocytes and other host cells and exhaust lymphocytes by polyclonal activation.[20] Related parasites can cleave host immunoglobulin attached to their surface into bound F_{ab} and free F_c components, covering antigenic sites but aborting further cell- or complement-mediated defenses.[21] Some intriguing cysticercal defense mechanisms are not immune-related;

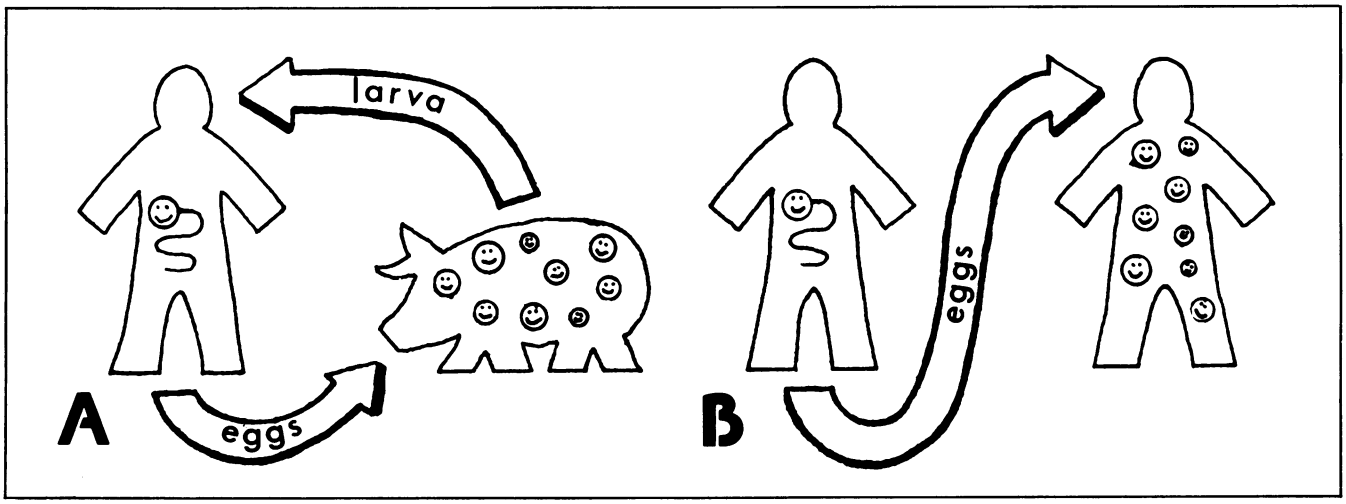

Figure 1.—Life cycle of *Taenia solium.* **A,** Taeniasis (infection with pork tapeworm) results when humans eat larvae in poorly cooked pork. Eggs passed in feces are then eaten by pigs, with release and migration of larvae (swine cysticercosis) completing the normal life cycle. **B,** Cysticercosis results when tapeworm eggs are ingested by another human, leading to diffuse infection with larvae. Autoinfection is possible by the fecal-oral route or (it is postulated) by reverse peristalsis of tapeworm segments into stomach, where eggs are released.

an example is the secretion of factors that inhibit host trypsin and chymotrypsin, thus preventing digestion while the embryo traverses the gut lumen.[22] Additionally, the fibrous capsule surrounding a cyst provides at least a partial physical barrier to host immune defenses.[20] These and other postulated mechanisms contribute to maintaining larval viability in the host (Figure 2). Apparently all these mechanisms are relatively specific for parasitic antigens or for the parasites' immediate vicinity in tissue (or both); there is no clinical or laboratory evidence for a generalized immunosuppression in patients who have cysticercosis.

When cysticerci die, their death prompts an intense inflammatory reaction. If current theories of immune interference are correct, this reaction stems not only from release of antigen by the dying worm, but also from a cessation of active immunosuppression. Onset or worsening of symptoms often coincides with this intense tissue response.[6] Confirmation of this natural history in living hosts is now available by sequential CT scanning.[23] Exacerbation of seizures, focal deficit or intracranial hypertension may be accompanied by CT findings of florid edema or contrast enhancement, which resolves over a course of weeks to months.

These observations lead to new perspectives on treatment. Insight into host immune defenses has stimulated considerable progress in developing vaccines, dependent primarily on an adequate supply of suitable antigen.[20] In a patient with already established infection, however, the question is whether killing the cyst is a good idea or a bad idea.[24]

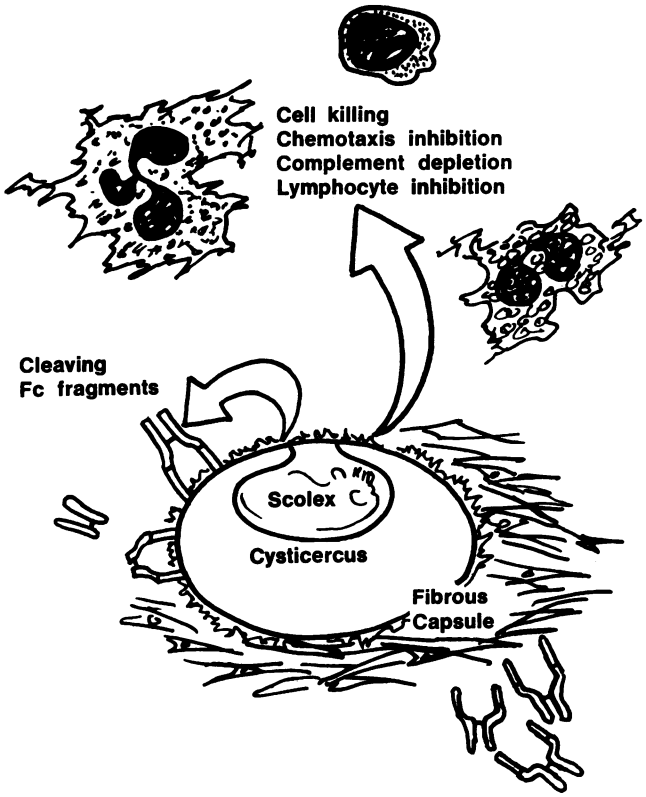

Figure 2.—Postulated mechanisms that promote survival of the cysticercus in an immunocompetent host. See text for details.

Several agents have been developed that are effective against cysticerci both in vitro and in vivo, most notably praziquantel.[25] Initial uncontrolled experience has been favorable,[26-28] but controlled trials are needed for several reasons. First, by killing the larvae, host immune defenses will be released from active suppression, which may result in a harmful acute inflammatory response. The specter of iatrogenically creating a lethal encephalitis cannot be dismissed[27,28] but perhaps will be preventable with concomitant steroid administration. Children should probably be treated more cautiously because of their predisposition to the encephalitic form[29] and to reactive brain swelling in general. Second, we now know that the larvae are often dead when a patient presents with symptoms. In this setting, the only value of praziquantel will be to eliminate any remaining viable worms. Last, the most debilitating symptoms result from chronic inflammation around nonviable cysts—a long-term process that may be unaffected or even accelerated by this therapy. In early trials praziquantel has already been noted to acutely worsen the meningitic response.[28]

As McCormick has suggested,[30] taeniacidal therapy may be more useful in certain clinical subgroups. Multiple parenchymal lesions may provide the best rationale for therapy. The patients with meningitis and hydrocephalus have the most refractory clinical course, but because their chronic inflammatory response is usually directed against already-lifeless cysts, they probably have the least to gain from larvicides. In a recent two-year follow-up on 100 patients receiving praziquantel, 16 deaths were recorded, of which 14 were apparently directly due to complications of continued subarachnoid inflammation.[31,32] Although the overall results included 40% cured and 43% at least slightly improved, our experience[1] and that of others[2-5] confirm the benign natural history of cysticercosis in most patients. Praziquantel therapy probably improves somewhat on this natural history, but the effect is hard to demonstrate.

Recently praziquantel has been released in the United States, approved for the treatment of other parasitic diseases. In our initial experience the drug is well tolerated. At least in adult patients, toxic effects of worm death have responded well to empirical steroid coverage. Unless patient and family compliance is virtually guaranteed, admission to hospital is appropriate at least for the first several days of therapy.

Another new and alarming perspective is epidemiologic: the documentation of transmission within the United States, as evidenced by the Los Angeles County series where seven patients had never left this country.[2] According to current knowledge, the establishment of new permanent foci in the US should not occur without infection of the pig population as well. This appears unlikely, at least in urban environments. Nevertheless, tapeworms are long-lived and usually produce no symptoms, and a single human carrier could serve as a

cysticercosis vector for many years.[33] Clearly, this issue merits careful public health consideration.

In summary, cysticercosis holds both threat and promise to our society. The threat is of a disease that causes major human and economic ravages in the Third World, now gaining a foothold in the United States, where it shows the potential to become endemic. The promise is that by studying this disease we can help lighten a major economic burden on the underdeveloped countries and learn more about the complex relationship between infection and immunosuppression—now of urgent interest for other reasons.[34] The newfound importance of this disease in the United States serves as continuing testimony to the interdependence of developed and developing countries.

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